sequence selected from: LeuCysPheArgMetLysAsp (residues 8-14 of SEQ ID NO:2); ValLeuTyrLeuHisAsn (residues 19-24 of SEQ ID NO:2); GlnLeuLeuAlaGly (residues 26-30 of SEQ ID NO:2); IleSerValValProAsn (residues 43-48 of SEQ ID NO:2); SerProValIleLeuGlyVal (residues 56-62 of SEQ ID NO:2); GlnCysLeuSerCysGlyThr (residues 67-73 of SEQ ID NO:2); ProIleLeuLysLeuGlu (residues 77-82 of SEQ ID NO:2); PheTyrArgArgAspMetGly (residues 101-107 of SEQ ID NO:2); LeuThrSerSerPheGluSer (residues 108-114 of SEQ ID NO:2); PheLeuCysThrSer (residues 121-125 of SEQ ID NO:2); GlnProValArgLeuThr (residues 130-135 of SEQ ID NO:2); PheTyrPheGlnGln (residues 150-154 of SEQ ID NO:2); ArgAlaLeuAspAlaSerLeu (residues 49-55 of SEQ ID NO:2); or GlyLeuHisAlaGluLysVal (residues 31-37 of SEQ ID NO:2); or B) specifically binds polyclonal antibodies generated against a 12 consecutive amino acid segment of SEQ ID NO: 6, 13, or 15; and comprises at least one sequence selected from: SerLeuArgHisValGlnAsp (residues 13-19 of SEQ ID NO:6); ValTrpIleLeuGlnAsn (residues 24-29 of SEQ ID NO:6); IleLeuThrAlaVal (residues 31-35 of SEQ ID NO:6); IleThrLeuLeuProCys (residues 46-51 of SEQ ID NO:6); AspProThrTyrMetGlyVal (residues 63-69 of SEQ ID NO:6); SerCysLeuPheCysThrLys (residues 74-80 of SEQ ID NO:6); ProValLeuGlnLeuGly (residues 85-90 of SEQ ID NO:6); PheTyrHisLysLysSerGly (residues 109-115 of SEQ ID NO:6); ThrThrSerThrPheGluSer (residues 116-122 of SEQ ID NO:6); PheIleAlaValCys (residues 129-133 of SEQ ID NO:6); CysProLeuIleLeuThr (residues 138-143 of SEQ ID NO:6); PheGluMetIleVal (residues 154-158 of SEQ ID NO:6); GlnAspLeuSer (residues 18-21 of SEQ ID NO:6); ValProArgLysGluGlnThrVal (residues 35-42 of SEQ ID NO:6); SerLysGlySerCysPro (residues 134-139 of SEQ ID NO:6); ArgAlaAlaSer (residues 8-11 of SEQ ID NO:6); ProCysGlnTyrLeuAspThrLeuGlu (residues 50-58 of SEQ ID NO:6); and SerGlyThrThr (residues 114-117 of SEQ ID NO:6); or ITGTIND (residues 23-29 of SEQ ID NO:13); VWTLQG (residues 34-39 of SEQ ID NO:13); NLVAV (residues 41-45 of SEQ ID NO:13); VAVITC (residues 56-61 of SEQ ID NO:13); DPIYLGI (residues 73-79 of SEQ ID NO:13); MCLYCEK (residues 84-90 of SEQ ID NO:13); PTLQLK (residues 95-100 of SEQ ID NO:13); FYRAKTG (residues 119-125 of SEQ ID NO:13); RTSTLES (residues 126-132 of SEQ ID

B' cont.

NO:13); FIASS (residues 139-143 of SEQ ID NO:13); QPIILT (residues 147-152 of SEQ ID NO:13); FELNI (residues 163-167 of SEQ ID NO:13); SMCK (residues 18-21 of SEQ ID NO:13); NDLN (residues 28-31 of SEQ ID NO:13); [VPR(R/S)TSVT] VPRRTSVT (residues 45-51 of SEQ ID NO:13); TCKYPEALE (residues 60-68 of SEQ ID NO:13); TGRT (residues 124-127 of SEQ ID NO:13); or SKGDQP (residues 143-148 of SEQ ID NO:13), or VPRSDSVT (residues 45-52 of SEQ ID NO:15); SKRDQP (residues 143-148 of SEQ ID NO:15). Preferred embodiments include such a polypeptide: wherein the polypeptide comprises a plurality of the described sequences. Preferably the 12 consecutive amino acid segment comes from an IL-1δ sequence (see SEQ ID NO: 2): LeuCysPheArgMetLysAspSerAlaLeuLysValLeuTyrLeuHisAsnAsn (residues 8-25 of SEQ ID NO:2); IleSerValValProAsnArgAlaLeuAspAlaSerLeuSerProValIleLeuGlyValGln (residues 43-63 of SEQ ID NO:2); SerProValIleLeuGlyValGlnGlyGlySerGlnCys (residues 56-68 of SEQ ID NO:2); ProIleLeuLysLeuGluProValAsnIleMetGluLeu (residues 77-89 of SEQ ID NO:2); ThrSerSerPheGluSerAlaAlaTyrProGlyTrpPhe (residues 109-121 of SEQ ID NO:2); PheLeuCysThrSerProGluAlaAspGlnProVal (residues 121-132 of SEQ ID NO:2); ThrGlnIleProGluAspProAlaTrpAspAlaProIle (residues 135-147 of SEQ ID NO:2); or ThrSerSerPheGluSerAlaAlaTyrProGlyTrpPhe (residues 109-121 of SEQ ID NO:2); or a rodent IL-1ε sequence (see SEQ ID NO: 6): ArgAlaAlaSerProSerLeuArgHisValGlnAspLeu (residues 8-20 of SEQ ID NO:6); SerSerArgValTrpIleLeuGlnAsnAsnIleLeu (residues 21-32 of SEQ ID NO:6); ProValThrIleThrLeuLeuProCysGlnTyrLeu (residues 43-54 of SEQ ID NO:6); GlyValGlnArgProMetSerCysLeuPheCysThr (residues 68-79 of SEQ ID NO:6); PheCysThrLysAspGlyGluGlnProValLeuGlnLeu (residues 77-89 of SEQ ID NO:6); ThrSerThrPheGluSerAlaAlaPheProGlyTrpPhe (residues 117-129 of SEQ ID NO:6); or CysSerLysGlySerCysProLeuIleLeuThrGln (residues 134-144 of SEQ ID NO:6); or a primate IL-1ε sequence (see SEQ ID NO: 13 or 15): SMCKPITGTINDL (residues 18-30 of SEQ ID NO:13); NQQVWTLQGQNL (residues 31-42 of SEQ ID NO:13); PVTVAVITCKYP (residues 53-64 SEQ ID NO:13); GIQNPEMCLYCE (residues 78-89 of SEQ ID NO:13); YCEKVGEQPTLQL (residues 87-99 of SEQ ID NO:13);

B' cont.

B' cont. TSTLESVAFPDWF (residues 127-139 of SEQ ID NO:13); SKGDQPIILTSE (residues 143-154 of SEQ ID NO:13); SKRDQPIILTSE (residues 143-154 of SEQ ID NO:15);or GKSYNTAFELNIND (residues 156-169 of SEQ ID NO:15).--

Please replace the paragraph on page 13, lines 3-11, and replace with the following rewritten paragraph:

B2 -- Figure 1A is a cartoon depicting a top down view through the central axis of the predicted IL-1δ or IL-1ε protein demonstrating the characteristic tertiary ß-trefoil structure with its 3-fold symmetric topology. Contact sites of the IL-1δ or IL-1ε protein that are predicted to bind the IL-1 receptor subunits are designated as sites A, B or C (Fig. 2). Contact sites A and C bind to the first receptor subunit of IL-1, while contact site B binds to the IL-1 second receptor subunit.--

Please replace the paragraph on page 16, lines 21-22, and replace with the following rewritten paragraph:

B3 --Table 4 shows relationship of IL-1 family members, and Fig. 2 provides an alignment of selected family members.--

Please delete the paragraph (Table 5) on page 24, lines 1-45. ✓

Please add the following new paragraph on page 13, after line 16:

B4 --Figs. 2A and B describe polypeptide sequences in the IL-1 family of cytokines. The position numbers refer to alignment, and are not residue numbers from the individual sequences. Various sites for interaction with receptor are: SITE A includes residues corresponding to positions numbered 16-19, 25-27, 32, 34-41, and 44; SITE B includes residues corresponding to positions numbered 9-12, 14, 52-60, 115, 117-118, 122-123, 168, and 170; and SITE C includes residues corresponding to positions numbered 84-109. B conformations correspond to positions 11-17; 22-27; 30-34; 48-53; 65-71; 77-83; 88-93;

110-117; 122-128; 135-139; 145-150; and 168-172. The sequences can be found in the sequence listing, as indicated: hIL-1ε (SEQ ID NO:15); mIL-1ε (residues 4-160 of SEQ ID NO:6); mIL-1δ (residues 3-160 of SEQ ID NO:2); hIL-1RA (residues 31-177 of SEQ ID NO:7); hIL-1γ (residues 37-193 of SEQ ID NO:8); mIL-1γ (residues 36-192 of SEQ ID NO:9); hIL-1β (residues 117-269 of SEQ ID NO:10); hIL-1α (residues 127-271 of SEQ ID NO:11)--

B4 cont.

Please replace the paragraph on page 40, lines 16-30, with the following re-written paragraph:

--The present invention particularly provides muteins which act as agonists or antagonists of the IL-1δ or IL-1ε. Structural alignment of mouse IL-1δ and mouse IL-1ε with other members of the IL-1 family show conserved features/residues, particularly 12 β strands folded into a β-trefoil fold (see Fig 1A; Table 3 and Fig.2A,B). The 12 mouse IL-1δ β strand domains are recited respectively (Table 3) as Leu8-Asp14, Val19-Asn24, Leu27-Gly31, Ile43-Asn48, Ser56-Val62, Gln67-Thr73, Pro77-Glu82, Phe99-Met106, Leu108-Ser114, Phe121-Ser125, Gln130-Thr135, and Gln153-Asp156 of SEQ ID NO: 2; while the 12 mouse IL-1ε β strand domains are recited respectively (Table 3) as Ser13-Asp19, Val24-Asn29, Ile31-Val35, Ile46-Cys51, Asp63-Val69, Ser74-Lys80, Pro85-Gly90, Ser107-Ser114, Thr116-Ser122, Phe129-Cys133, Cys138-Thr143, and Ile157-His160 of SEQ ID NO: 6).--

B5

Please replace the paragraph on page 40, lines 31-37 and continuing to page 41, lines 1-2, with the following rewritten paragraph:

--Alignment of the mouse IL-1δ and IL-1ε sequences (using the Met initiation residue as the first amino acid) with other members of the IL-1 family indicates that the β conformations correspond to similar sequences in other IL-1 family members (see Tables 3, 4, and Fig.2A,B). See also, Bazan, et al. (1996) Nature 379:591; Lodi, et al. (1994) Science 263:1762-1766; Sayle and Milner-White (1995) TIBS 20:374-376; and Gronenberg, et al. (1991) Protein Engineering 4:263-269.--

B6

Please replace the paragraph on page 42, lines 7-14, and replace with the following rewritten paragraph:

--The corresponding location in rodent IL-1δ or IL-1ε (between β4 and β5) defines a domain that forms a polypeptide loop which is part of a primary binding segment to the IL-1 receptor type (site B in Fig.2A,B). The loop, depicted pictorially in Figure 1A as protruding into the central axis of the mature IL-1δ or IL-1ε protein, is located between arrows 4 and 5). More precisely, the loop is defined for IL-1δ by amino residues Pro47-Ala53 of SEQ ID NO: 2 and for IL-1ε by amino residues Pro50-Glu58 of SEQ ID NO: 6. Accordingly, IL-1δ or IL-1ε antagonist activity should be generated by removal all or an appropriate portion of a corresponding portion of amino acids located between β4 and β5. This suggests that analogous modifications to the loop between the β4 and the β5 strands will lead to variants with predictable biological activities. With mouse IL-1RA, it was shown that replacement of the mouse IL-1RA residues with those mouse IL-1β residues introduced IL-1 activity to the IL-1RA variant (IL-1RA could then bind type III receptor). Similar substitutions will establish that type III receptor can probably be used by mouse IL-1δ or IL-1ε proteins or muteins. Additional site B contacts are defined in rodent IL-1δ by amino residues 8-11, 13, 112, 114-117, 158 and 160 of SEQ ID NO: 2. Corresponding additional site B contacts are defined in mouse IL-1ε by amino residues 3-6, 8, 104, 106-109, 154 and 156 of SEQ ID NO: 6. Corresponding residues should be important in the primate sequence (see SEQ ID NO: 13 and 15).--

B7

Please replace the paragraph on page 42, lines 35-36 and continuing to page 43, lines 1-10, and replace with the following rewritten paragraph:

--Sites A and C (see Fig. 2A,B) mediate binding of IL-1δ or IL-1ε to the first IL-1 receptor subunit, e.g., an alpha receptor subunit. Site A contacts correspond in IL-1δ to amino residues 13-16, 22-24, 29, 31-37, 39, 126-131, 151, and 153 of SEQ ID NO: 2; while site C contacts correspond in IL-1δ to amino residues 74-98 of SEQ ID NO: 2. Site A contacts are defined in IL-1ε by amino residues 18-21, 21-29, 33, 35-

B8